EUNETHYDIS - Searching for valid aetiological candidates of Attention-Deficit Hyperactivity Disorder of Hyperkinetic Disorder

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ORIGINAL CONTRIBUTION

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EUNETHYDIS – Searching for valid aetiological candidates of Attention-Deficit Hyperactivity Disorder or Hyperkinetic Disorder

Abstract *Background* To step up research in ADHD, exchange of ideas, working together on key theoretical models and cooperative studies are necessary. *Objective* To report about a European approach with strong links to the rest of the world. *Method* European Network on Hyperkinetic Disorders (Eunethydis) studies of Attention - Deficit Hyperactivity Disorder (ADHD) or Hyperkinetic Disorder (HKD) is briefly reviewed in the context of the international effort to discover the aetiology of the disorder. *Results* There are promising neurobiological, neurophysiological and neuropsychological candidates to explain the nature of ADHD/HKD. *Conclusion* Eunethydis has shown to be a fruitful platform for ADHD research and has good resources for its further development.

Key words ADHD – HKD – executive functioning – inhibition – working memory – arousal – cognitive-energetic – delay aversion – frontal lobe – cerebellum – review

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Eunethydis

Eunethydis (European Network on Hyperkinetic Disorders) is a group of child psychiatrists, paediatricians, psychologists, neurologists and neuroscientists who gather annually to discuss research in Attention-Deficit Hyperactivity Disorder (ADHD) or Hyperkinetic Disorder (HKD) and work on key theoretical models of ADHD/HKD [65]. Eunethydis explicitly attempts to forge theoretical links between clinical and fundamental science. This paper briefly sketches the main neurobiological models used by Eunethydis. The paper has a cognitive neuroscience character and will, therefore, not deal with clinical science issues of taxonomy [27], epidemiology [20] longitudinal research [96] or treatment studies in Europe [17].

Neurobiology of ADHD

One of the main contributions of Eunethydis to the field has been to encourage the development of neurobiological models and mechanisms of HKD/ADHD. The primary model from this work proposes that ADHD/HKD is due to hypofunctioning of dopamine (DA), which produces altered reinforcement processes and deficient extinction [65, 66]. A key mechanism involved in reinforcement process is the nucleus accumbens [56]. An alternative "hyper"–"hypo" model of DA has also been proposed [52]. Hypofunctioning of DA is thought to give rise to delay aversion, impulsiveness, deficient response suppression and increased behavioural variability. The dopaminergic hypothesis of ADHD/HKD is crucial to both animal and molecular genetic studies of ADHD and explaining methylphenidate's therapeutic effect.

One candidate mechanism is how perinatal anoxia and dopamine relate. Brake, Sullivan, & Gratton [9] found that, while the left prefrontal cortex (PFC) DA response was unaffected by perinatal anoxia, the right PFC response was dramatically suppressed. Moreover, dopamine transporter (DAT) levels were elevated selectively in the right PFC.

The Naples group [22] identified an epigenetic mechanism [41] suggesting that tyrosine hydroxylase and dopamine transporter gene expression are significantly and transiently reduced in one rat ADHD model (SHR) midbrain during the first month of postnatal develop-

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ment. High-affinity DA uptake activity was significantly reduced in synaptosomes from the striatum of 1-month-old SHR compared to controls. Down-regulation of DA neurotransmission occurs in the midbrain of this ADHD animal model in a developmentally regulated temporal window during postnatal development. These findings suggest that epigenetic factors acting during critical periods of post-natal development may interact with genetic determinants in ADHD.

The dopamine dysfunction hypothesis has led to the search for candidate dopamine gene(s) encoding the dopamine transporter. Currently, several Eunethydis centres are involved in the international molecular ADHD genetic study (Image) led by Dr S. Faraone. Previously, Faraone, Doyle, Mick & Biederman [19] performed a meta-analysis of case-control and family-based studies. Faraone et al. found a small association between ADHD and the dopamine receptor gene D_4 (DRD_4). Mill et al. [46] genotyped five polymorphisms across D_4 and noted that a haplotype of markers may confer susceptibility to ADHD, confirming another meta-analysis of the involvement of dopamine system genes in ADHD [44]. Holmes et al. [30] reported that DRD_4 was significantly associated with ADHD children comorbid for Conduct Disorder (CD). While this search for candidate genes for ADHD is given considerable interest, it is unclear in how far the candidates are specific for ADHD/HKD or are also associated with a region implicated in autism [84].

Behavioural genetics and cognition

The dopamine-dysfunction hypothesis in ADHD/HKD has inspired research into the relation between cognitive performance, particularly response suppression, and molecular as well as behavioural genetics [42]. Swanson et al. [93] examined the relation between the 7-repeat allele of the dopamine receptor D_4 gene and cognitive neuropsychological performance. No relation was found between the 7-repeat and inhibitory deficits in ADHD, possibly due to the small sample size. However, Kuntsi & Stevenson [37] found in a twin study that variability of speed on the Stop Signal task [53] was associated with genetic effects on extreme hyperactivity ratings, and a significant proportion was shared with the genetic effects on the variability in speed of processing. This latter variable emerged most consistently and was the best discriminator between the hyperactive and control groups in the non-genetic analyses [38]. Using a familial design Crosbie and Schachar [16] also found deficient response inhibition to be a possible marker of familial ADHD. In a sib-proband study, Slaats-Willemse et al. [82] found that non-affected siblings of ADHD probands had response inhibition deficits, but that their performance on the inhibition measures did not significantly differ from their siblings with ADHD.

The hunt for ADHD genes and their relation to cognitive neuropsychological characteristics of ADHD/HKD is now in full swing in various European centres and in the coming ten years significant relationships may be expected to be found.

Neurophysiological mechanisms and neuroanatomy

Neurophysiological research in ADHD/HKD originally sought to determine the arousal/activation deficit in ADHD [68], stimulus seeking behaviour [1] and, recently, whether disinhibition of the nervous system can explain ADHD/HKD [51]. A variety of techniques have been used to reach these goals. Power spectrum analysis indicated less right lateralized asymmetry in ADHD boys than in ADHD girls [6]. Both event-related potential (ERP) paradigms and whole head analyses of the electroencephalogram (EEG) with low-resolution electromagnetic tomography (LORETA) have been used in several studies of ADHD/HKD children [10]. The ERP research indicated that ADHD have reduced motor preparation [26], and reduced P300 to both cued and non-cued targets [31, 40, 54] suggesting under activation of the posterior attention system in ADHD/HKD children [4].

Additional evidence has been found that children with HKD have reduced P300 amplitudes to cues and distracters suggesting a deficiency in attentional orienting/inhibition [4]. Global field power of the cue-CNV microstate related to anticipation and preparation was reduced in HKD but not in children comorbid for HKD and CD (HKD-CD). Reduction in global power is consistent with a model that HKD children (without ODD/CD) suffer from an energetical state dysregulation [75] rather than only a response suppression deficit [5]. Subsequent analysis demonstrated that HKD children but not children with HKD-CD were impaired in processing a signal requiring motor preparation [4]. ERP paradigms differentiate ADHD/HKD from ADHD/HKD comorbid for CD or Tic disorder [61, 103] consistent with MRI studies of ADHD and Tourette syndrome [32]. ERP research has successfully shown the therapeutic effects of methylphenidate in ADHD as effecting central and motor output processes [31] and differentiates methylphenidate from desipramine and l-dopa [55].

Another window into inhibition in ADHD has been to use transcranial magnetic stimulation (TMS). Moll et al. [47] found reduced intracortical inhibition in ADHD children but not in the cortical silent period, suggesting a specific inhibition, motor dysfunction in ADHD. This finding is consistent with structural MRI findings of smaller basal ganglia volumes in ADHD children [2, 11, 12, 21, 97] and smaller cerebellar volume in ADHD [7].

Developmental transitions in brain structure and function may be crucial in ADHD. For example, the caudate nucleus differences between ADHD and control children disappear in mid adolescence [14]. Amplitude reductions of brain electric visual evoked potentials and high ratio of slow frequencies in standard EEG have been found to normalize from eight to thirteen years, suggesting that it is only later that the sensory pathways of hyperkinetic children presumably reach the same functional level as that of healthy children [60]. It remains to be determined whether reduced intracortical inhibition in ADHD follows a similar developmental path and cannot be considered a biological marker of ADHD [13]. Further, differences in imaging technique are producing different results between centres. In contrast to the reduction in volume reported in earlier studies, more recent work is showing that an *enlarged* superior frontal lobe is correlated with higher hyperactivity scores [91]. The significance of these results remains to be determined.

Finally, sleep research in ADHD has gained the insight that a forced ultradian cycling appears characteristic for the sleep of children with ADHD, which may be related to alterations of brain monoamines and cortical inhibitory control [33].

Neuropsychological mechanisms

Recent reviews have summarized the two main goals of neuropsychological research in ADHD as: (1) determination of the neural networks in the disorder and (2) establish the specificity of the neuropsychological dysfunction [77]. The five candidate neuropsychological mechanisms of ADHD are a prefrontal inhibition dysfunction [5], working memory/selective attention dysfunction [13, 94], a timing/motor deficit [63, 64] and a deficiency of state regulation [75]. These candidates are briefly discussed below.

There has been a systematic evaluation of the inhibition hypothesis from preschool [90] to school-aged children [69]. More than 20 studies of the Stop Signal Task [43] have been published indicating that ADHD children have a longer, variable, inhibitory function than controls but this finding is not specific to ADHD but is common to ODD and CD [53]. Furthermore, both children with a fast-guess reading style [72] and children with Higher Function Autism (HFA) have also been demonstrated to have poorer Stop Signal Task performance than controls [23] and HFA to have this more than children with Tourette's syndrome [101]. Rubia et al. [63] found that the right prefrontal cortex and left caudate nucleus showed less activation in ADHD patients than controls. Taken together these results support an inhibition deficit hypothesis in ADHD/HKD but this is not specific to ADHD or to externalizing disorders. Scheres et al. [70] demonstrated that the disinhibition effect did not generalize to other forms of inhibitory control, suggesting that a generalized loss of inhibition in ADHD is not an adequate account of ADHD [5]. This result is consistent with the TMS study that methylphenidate enhances intracortical facilitation but not intracortical inhibition [48]. Solanto et al. [86] demonstrated that in addition to inhibition, delay aversion could explain independent variance [89]. This finding has led to a reformulated model of ADHD in which both delay aversion and inhibition are conceived of as dual pathways in ADHD [87, 88].

Two key candidates in ADHD research are, first, the relation between attention and Working Memory and, second, the relation between inhibition and response conflict. Nigg [51] proposed that inhibition deficits in HFA might be explained by WM, whereas in ADHD inhibition deficits can be better explained by a motor dysregulation [5]. Geurts et al. [23] found that this intriguing dichotomy did not hold up in an executive function study of both children with HFA and ADHD. A recent meta-analysis of response conflict, as measured by the Stroop, indicates that Stroop response conflict is an unattractive measure in ADHD [49]. It remains to be determined whether specific working memory candidates can be discovered which can separate ADHD from HFA children.

One explanation of ADHD has been that performance deficits are due to poor selective attention [18]. Early research defined selective attention as a limitation in the rate of controlled processing located in short-term memory [71, 80]. This definition led to a series of studies using both a memory and visual load paradigm [74]. The conclusion from that research programme was that ADHD children did not suffer from a selective attention deficit (see for review [73]). Hence, a selective attention deficit does not appear to be implicated in ADHD.

The role of executive functions [57] and the frontal lobes [81] has been a candidate mechanism. However, MRI reports [7] and variability in timing [62, 63] have refocused research on the role of the cerebellum in ADHD [13, 85]. Response selection difficulties [45] as well as poor balancing have been noted in ADHD [58] suggesting possible cerebellar deficiency in ADHD. These findings have revived interest in minor neurological dysfunction [35, 99, 100] and differentiation of ADHD children from children with a neurological disorder [34]. In the near future, there may be an attempt to differentiate ADHD from HFA children [23] or children with clumsiness [25] via timing and cerebellar neuropsychological tasks. Alternatively, pragmatic dysfunction in both HFA and to a lesser degree in ADHD [24] suggests that this particular aspect of executive functioning may be relevant in some subgroups [95], although one study found no significant interactions be-

tween hyperactivity and Specific Language Impairment on any neuropsychological measure [102].

The cognitive energetic dysregulation hypothesis argues that ADHD performance deficits are due to non-optimal energetic allocation, which leads to dysfunctioning at either a specific energetic pool, at the motor stage of processing or at a higher level of executive management [8, 73, 75]. This model can be traced to earlier work in which ADHD children were shown to be less physiologically aroused and faster habituators than normal controls [67]. Herpertz et al. [29] found recently that children with CD and ADHD + CD showed decreased electrodermal responses and accelerated habituation compared to children with ADHD alone and controls, thus suggesting possible energetic differences in externalizing disorders.

Differences in energetic allocation have been reported in response conflict tasks [59], which substantially effect responses inhibition in ADHD [83]. Sonuga-Barke [87] found in two studies that AD/HD children exhibited a quadratic performance function as predicted by the cognitive-energetic model of AD/HD. Steger et al. [92] found that in long intervals in a motor task revealed increased errors and onset variability. Using the Flanker task, Crone, Jennings and van der Molen [15] reported that ADHD children responded less accurately under the threat of punishment. Phasic heart rate did not differ between groups, but immediate reward feedback induced greater heart rate responses in control than in ADHD children. Inappropriate energetic allocation has also been observed in vigilance studies using EEG measures [3, 28]. Further gamma band responses showed a right lateral preference in ADHD children to both attended and non-attended stimuli, suggesting poor energetic allocation [104]. An interesting link between molecular genetic studies and the dopamine transporter (DAT) has been laid by a review of SPECT studies in adult ADHD patients: Patients with ADHD and with a history of nicotine abuse both displayed lower values of DAT density in SPECT than non-smokers with ADHD. DAT seem to be elevated in non-smoking ADHD patients suffering from the purely inattentive subtype of ADHD as well as in those with the combined or purely hyperactive/impulsive subtype [36]. Thapar et al. [98] reported that, although genetic influences accounted for most of the variance in offspring ADHD, maternal smoking during pregnancy accounted for a significant environmentally mediated association. This suggests that ADHD patients may, in some cases, be employing nicotine as a method for self-therapy to compensate for their non-optimal energetic allocation and be related to brain activation patterns [50].

While ADHD is often suggested to be a good example of dysexecutive functioning [5], comparison of ADHD children with HFA suggests that HFA children have a much more profound and extensive deficit in executive functioning than ADHD children [23, 76, 79], although this may depend upon the age at which the child is tested [6, 90]. More work is required to determine norms for preschool severity in ADHD than currently available. It is clear that a much wider neural network in involved in ADHD than one specific to the prefrontal cortex and involves some features of WM, timing and energetic allocation [13, 77]. Differentiation of ADHD from correlated disorders such as dyscalculia [78], developmental coordination disorder [39], HFA, Tourette and Fragile-X syndrome is a matter of urgent study. The specific candidates have been described above and will be tested for their validity in future work associated with Eunethydis.

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